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Carotid Endarterectomy versus Carotid Angioplasty Cui Bono☆

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Abstract *Objectives:* To evaluate the current status of carotid angioplasty (CAS) versus carotid endarterectomy (CEA) in the management of patients with carotid bifurcation disease.
Design: Retrospective review of published and presented prospective randomized trials to date, regarding comparative results of CAS versus CEA.
Materials: Review of six published prospective randomized trials, one trial presented in press, and one trial completed and being analyzed. Large population based studies and a comparative registry study are also included.
Methods: Retrospective literature review.
Results: The results today favor CEA over CAS with respect to stroke morbidity, mortality, freedom from recurrence, and cost.
Conclusions: At the present time, CEA remains the intervention of choice in the management of carotid bifurcation disease.
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Carotid endarterectomy is a well established intervention for patients with occlusive disease of the carotid bifurcation. Its efficacy for treatment of both symptomatic[1,2] and asymptomatic[3,4] patients has been well documented in multiple prospective randomized trials. Carotid stent/angioplasty is a new alternative that is currently undergoing evaluation. Individual reported experience with stent/angioplasty as well as prospective registries have shown stroke morbidity and mortality rates that are competitive with results reported from NASCET and ACAS. However, it is a mistake to compare current angioplasty data with 20 year old carotid endarterectomy data. The results of carotid endarterectomy have progressively improved over the intervening time since these early trial results. These improvements are multifactorial and include better perioperative medical management with the use of statins, beta blockers, ace inhibitors, and anti-platelet agents. Techniques of carotid endarterectomy have also improved and, in particular, most surgeons performing carotid surgery have now had extended training in performing the operation beyond a basic surgical residency. For these reasons, the only way to determine the comparative merit of carotid angioplasty with carotid endarterectomy will be

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in the form of well monitored, properly designed, multi-institutional prospective randomized trials. Several trials have already been reported,[5–10] and two large trials have been completed and data are currently under analysis.[11,12] The objective of this report is to review the results of published or reported trials, to examine countrywide data bases that have been analyzed, and to describe the design and lead-in data from the CREST trial which will be the largest trial to date.

Prospective Trials Prior to Anti-Embolism Protection

The CAVATAS trial

The CAVATAS trial was a multi-institutional study carried out primarily in the UK. It was begun in 1992. Five hundred four patients, primarily with symptomatic carotid artery disease were randomized between angioplasty (CAS) and carotid endarterectomy (CEA). The results showed no difference in the 30 day complication rates of death and stroke, 10% for CAS and 9.9% for CEA.[5] Both of these rates are unacceptably high by current standards and are only of historical interest. However, the trialists also studied the incidence of early and late recurrence of stenosis. At one year, the re-stenosis rate for CAS was 10.5% versus 2.5% for CEA.[13]

The Leicester trial

This was meant to be a single institution prospective randomized trial. The trial was stopped after only 17 patients were randomized for reasons of safety concerns. Ten patients underwent CEA without death or stroke. Seven patients underwent CAS with 5 strokes, 3 of which were disabling.[6]

The Schneider wall stent trial

This was a multi-institutional prospective randomized trial that was designed to enter 700 symptomatic patients with stenoses ranging from 60 to 99%. However, the trial was stopped by the data and safety monitoring committee after only 217 patients were randomized. The one-year combined death and stroke rate for CAS was 12.1% versus 3.6% for CEA. The difference was highly statistically significant with $p < 0.02$.[7]

Prospective Randomized Trials after Anti-Embolism Protection

The introduction of embolism protection devices was designed to reduce the incidence of embolic stroke associated with balloon angioplasty. Experimental studies have documented the capture of athero-embolic fragments using these devices. Interestingly there have been no clinical studies that demonstrate a stroke risk reduction with the use of embolic protection devices. Nonetheless it is intuitive and it has been taken for granted that they represent a valuable adjunct.

The Sapphire trial

Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy (SAPPHIRE) was a trial with 3 arms. There was a registry for CAS and a registry for CEA in patients who did not wish to be randomized and a prospective randomized trial for those who were willing to be randomized. The Angioguard filter and Precise stent were used in the CAS arms of the trial. The two registries are of minimal interest. The randomized trial consisted of only 307 patients with either symptomatic carotid stenosis >50% or asymptomatic patients with stenoses >80%. High risk was defined as a patient with multiple medical co-morbidities or difficult surgical access such as a radiated neck, prior carotid surgery, a high lesion, tracheotomy, etc. The traditional endpoints of stroke and death were included, but for the first time in a carotid trial, myocardial infarction was added as a primary endpoint. Furthermore, non-Q wave myocardial infarction received equal weight as an endpoint. Of the total of 307 patients, 156 underwent CAS and 151 underwent CEA. There was no difference in the combined endpoints of death and stroke, 4.5% for CAS and 6.6% for CEA. However, when myocardial infarction was added to death and stroke, the combined endpoints reached a statistically significant difference favoring CAS. The combined endpoints were 5.8% for CAS and 12.6% for CEA at the end of 30 days.[8] These differences held for 1 year, but by four years, there was no difference between the two groups when considering freedom from stroke, freedom from death, and freedom from major adverse events.[14] There have been several criticisms of this study which include a small sample size and providing equal endpoint value of non-Q wave MI to death and stroke.

The EVA 3S study (endarterectomy versus angioplasty in patients with severe symptomatic carotid stenosis)

The EVA 3S study was a large multi-institutional prospective randomized trial carried out in France. Symptomatic patients with hemodynamically significant carotid stenosis were randomly allocated to CAS or CEA. After 527 patients were randomized, the study was stopped by the data and safety monitoring committee. The combined death and stroke rate for CEA was 3.9% whereas the rate for CAS was 9.6%. These differences were statistically significant and clearly favored CEA as the safer procedure.[9] The EVA 3S investigators also reported their data after 4 years. The four year ipsilateral stroke rate was 11.1% in CAS versus 6.2% in CEA. The combined four year death and stroke rate was 26.9% in CAS versus 21.6% in CEA, once again favoring CEA over CAS after four years of follow-up.[15] This study was criticized by the interventional community in the United States who implied that those who did the CAS procedure were not sufficiently experienced and that this led to a higher complication rate. In a post-hoc analysis, the authors separated out the ''high volume'' interventionists from those with lower volume experience in order to compare their results. There was no difference between the two groups performing CAS.

The SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy) Trial. This was a multi-institutional prospective randomized trial

Table 1 Recent trial comparative data CEA versus CAS.

Trial	Risk category	Symptomatic status	CEA: 30-day death plus stroke	CAS: 30-day death plus stroke	*p* value
Sapphire	High	Symptomatic	10.3%	2.1%	NS
Sapphire	High	Asymptomatic	6.1%	5.2%	NS
EVA-3S	Average	Symptomatic	3.9%	9.6%	0.01
Space	Average	Symptomatic	6.5%	7.7%	NS
ICSS	Average	Symptomatic	5.1% incl. MI	8.5% incl. MI	0.004

carried out in Germany, Austria, and Switzerland in which symptomatic patients with high grade carotid stenosis were randomly allocated to either CAS or CEA. The hypothesis of the trial was that CAS was not inferior to CEA and the statistical analysis was applied accordingly. The trial was stopped prematurely because a futility analysis revealed that further addition of patients was unlikely to reach an endpoint. At the time the trial was stopped, the 30 day death and stroke rate for CAS was 7.7% and 6.5% for CEA. The conclusion was that the trial failed to prove that CAS was not inferior to CEA.[10] The trialists also reported upon the 2 year incidence of recurrent stenosis >70%. The incidence following CAS was 10.7% versus 4.6% after CEA.[16]

The International Carotid Stenting Study (ICSS)

The ICSS study and results were presented at the European Stroke Conference held in Stockholm, Sweden on May 28th, 2009. The study involved 50 centers in 15 countries. The report has not yet been published. This is the largest trial reported to date. Seventeen hundred and ten patients with symptomatic, high grade carotid stenoses were randomly allocated to either CAS or CEA. Eight hundred fifty three patients underwent CAS and 857 patients underwent CEA. The endpoints included stroke, MI, and death within 30 days. In an intension to treat analysis, the incidence was 8.5% in the CAS group versus 5.1% in the CEA group ($p = 0.004$). When the results were subjected to a per protocol analysis, the incidence was 7.4% in the CAS group and 4% in the CEA group ($p = 0.003$).[11]

These results, when confirmed by peer review, clearly will favor CEA as the procedure of choice for symptomatic patients with high grade carotid stenosis. The recent randomized trial data are summarized in Table 1.

The CREST (carotid revascularization endarterectomy versus stenting) trial

The patient input was completed one year ago and the one year data are currently being analyzed. When reported, this will be the largest trial to date. Two thousand five hundred and two patients (1321 symptomatic and 1181 asymptomatic) were randomly allocated to either protected balloon angioplasty and stenting or carotid endarterectomy. The design of this trial has several unique features. In recognition of the fact that the majority of patients undergoing CEA are asymptomatic, this study includes both symptomatic and asymptomatic patients. It is also stratified to be able identify any result differences related to gender. Finally, in order to address the issue regarding competence of those performing CAS, the interventional management committee first screened potential participants regarding angioplasty experience. Those who qualified after the initial review were required to prospectively submit up to 20 CAS patients that followed the CREST protocol and were subject to the same endpoint analysis. If the prospective participant demonstrated competence in this manner, then and only then, were they permitted to participate in randomization. Surgeons who wished to participate were screened by a surgical management committee using the criteria validated in the ACAS study.[12,17,18] CREST has received permission from the data and safety monitoring committee to report one year results. That analysis is currently underway and publication is anticipated in early 2010. In the meantime, data from the lead in phase of CREST have been reported regarding the results of CAS prior to randomization. First of all, the overall 30 day death, stroke, and MI rate in patients undergoing CAS was 5.1%. For asymptomatic patients, the rate was 4.9% and for symptomatic patients, the rate was 5.8%.[19] In addition, advancing age has an exponentially adverse effect on CAS complications. At 30 days, the death, stroke, and MI rate for CAS in patients less than 60 years of age was 2.2%, for patients 60–69, it was 2.5%, for patients 70–79, it jumps to 6.4%, and for patients over the age of 80, it jumps again to 13.9%.[20] It was also noted that bleeding complications associated with CAS had an adverse outcome following CAS. The incidence of hemorrhagic complications, usually at the femoral puncture site, was

Table 2 Population based studies.

Trial	Risk category	Symptomatic status	CEA: 30-day death plus stroke	CAS: 30-day death plus stroke	*p* value
NIS 2003/4	All	Asymptomatic	1.22%	2.24%	$p < 0.0001$
NIS 2003/4	All	Symptomatic	2.16%	11.7%	$p < 0.001$
SVS registry	All	Symptomatic	3.75% incl. MI	7.13% incl. MI	0.014
SVS registry	All	Asymptomatic	1.97%	4.6% incl. MI	0.003

7.3%. The death and stroke rate following CAS if there was a hemorrhagic complication was 19.6% versus 4.4% in the absence of hemorrhagic complications. In follow-up, the one year re-stenosis rate was monitored. At one year, 28% of CAS patients had a re-stenosis greater than 50%. Seven percent had a re-stenosis in the severe 80—99% category, and 0.3% had a total occlusion.

Population Based Studies

United States hospital discharge statistics 2003—2004

The NIS data base was sampled for the incidence of CEA and CAS as well as the complication rates of stroke and death for the years 2003 and 2004. There was a total of 259,080 patients undergoing carotid revascularization during that two-year interval. 245,045 (94.6%) underwent CEA and 14,035 (5.4%) underwent CAS. Ninety-two percent of the patients were asymptomatic and eight percent were symptomatic. The overall death and stroke rate for CAS was 3.4% whereas the overall death and stroke rate for CEA was 1.17%. The death and stroke rate in asymptomatic patients undergoing CAS was 2.24% versus 1.22% for CEA. In symptomatic patients, the death and stroke rate for CAS was 11.7% versus 2.16% for CEA.[21]

The SVS registry

Most registry data are industry supported and tend to be self serving. However CMS, the organization responsible for administering Medicare and Medicaid in the United States has mandated that all hospitals who wish to perform CAS must submit their data to an approved registry in order to track communitywide results. The Society for Vascular Surgery (SVS) has established an approved registry to which hospitals can submit their data. In addition, the SVS registry went one step further. They required that any hospital that wished to use their registry for submission of CAS results must also submit their CEA data. Thus the SVS data base provides the opportunity to compare the results of CAS with CEA from the same hospital pool. In their initial report, the SVS registry had 645 symptomatic patients who underwent CAS with a 30 day combined death, stroke, and MI rate of 7.13%. At the same time, 506 symptomatic patients underwent CEA with a combined death, stroke, and MI rate of 3.75% ($p = 0.014$). The registry also reported data on 805 asymptomatic patients undergoing CAS with a combined death, stroke, and MI rate of 4.6% versus 606 asymptomatic patients undergoing CEA with a combined death, stroke, and MI rate of 1.97% ($p = 0.003$).[22] The population based studies are summarized in Table 2.

Cost Analysis

In these days of escalating health care costs, the comparative cost of competing interventions, as well as comparative results, must be taken into consideration. The national hospital discharge data base for the year 2005 provides some insight into this issue. The average hospital charge for CEA in asymptomatic patients was $27,000. The average hospital charge for CAS in asymptomatic patients was $32,400. The average hospital charge for CEA in symptomatic patients was $37,000. The average hospital charge for CAS in symptomatic patients was $63,000.[23]

Conclusions

Based upon the current prospective randomized trial data and clinical utilization results, one must conclude that CAS carries a higher morbidity/mortality at a higher dollar cost than CEA. The results of CREST, when available, may change that conclusion. In the meantime, when asked cui bono (who benefits), one must conclude that the beneficiaries of CAS are the device manufacturers and interventionists. At this time the beneficiaries of CEA are surgeons and their patients.

Conflict of Interest

None.

Funding

None.

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